

# 脑小血管病性认知功能障碍的危险因素研究进展

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## 摘要

脑小血管病(cerebral small vessel disease, CSVD)是一组具有不同病理背景的各种血管疾病。脑血管的高级脉管系统网通常受到影响, 包括小动脉、微动脉、毛细血管、微静脉和小静脉。脑小血管疾病有几种分类: 其中包括Binswanger病、脑白质疏松症、脑微出血(CMBs)和腔隙性中风等疾病, 临床表现为认知功能下降、情感障碍等。脑小血管病性认知功能障碍是血管性认知障碍的重要亚型, 且认知功能障碍是脑小血管病最常见的临床表现。脑小血管病诱发认知功能障碍的危险因素可能涉及年龄、性别、肥胖等因素, 因此对脑小血管病性认知功能障碍的危险因素进行深入探讨, 可进一步提升和丰富脑小血管病性认知功能障碍的防治, 延缓疾病进展, 提高生活质量。

## 关键词

脑小血管病, 认知功能障碍, 危险因素, 研究进展

## Research Progress in Risk Factors for Cognitive Dysfunction in Cerebral Small Vessel Disease

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## Abstract

**Cerebral small vessel disease (CSVD) is a group of vascular diseases with different pathological backgrounds. The higher vasculature network of the blood vessel is usually affected by arterioles, arterioles, capillaries and venules. There are several categories of cerebral small vessel diseases including Binswanger's disease, leukoaraiosis, cerebral microbleeds (CMBs) and lacunar stroke, is mainly manifested as cognitive decline and emotional disturbance clinically. Small cerebral vascular cognitive dysfunction is an important subtype of vascular cognitive dysfunction, and cognitive dysfunction is the most common clinical manifestations of small cerebral vascular disease. The risk factors of cognitive dysfunction induced by small cerebral vascular disease may involve age, gender, obesity and other factors, therefore, the in-depth study of the risk factors of cerebral small vascular disease cognitive dysfunction can further improve and enrich the prevention and treatment of cerebral small vascular disease cognitive dysfunction, delay the disease progression, improve the quality of life.**

## Keywords

**Cerebral Small Vessel Disease, Cognitive Dysfunction, Risk Factors, Research Progress**

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## 1. 引言

脑小血管病(cerebral small vessel disease, CSVD)是一种慢性、进行性的小动脉、毛细血管和小静脉疾病, 主要供应白质和灰质深部结构; 它的特点是临床表现多样, 脑的神经影像学 and 神经病理学研究也有特殊变化[1] [2]。这些变化影响直径为 50~400 微米的小血管, 并导致皮质下脑结构的白质受损。脑小血管病是一种动态的疾病过程, 不仅限于脑血管, 而且影响全身。它具有临床异质性, 是最常见的脑血管病(CVD) [2]。脑小血管病约占所有中风的 20%, 包括 25%的缺血性中风和 45%的血管性痴呆[2] [3]。认知能力恶化的最常见原因是与两种主要疾病(阿尔茨海默病和脑小血管病引起的痴呆, 即血管性痴呆)相关的进行性、不可逆的神经元损伤。几十年来, 这些疾病被视为具有不同病因的不同疾病。然而, 近年来的研究表明, 脑小血管病标记物在被诊断患有 AD 的个体中很常见[4]。通过全面的临床(高血压、冠心病、糖尿病、高脂血症、体重指数、吸烟状况、饮酒量)和社会人口数据分析发现: 轻度认知障碍(MCI)中 73%的人与脑小血管病有关, 重度脑小血管病与 MCI 的发病率加倍相关[5]。慢性脑小血管病主要与进行性认知障碍有关(从轻度认知障碍到皮质下痴呆) [6] [7] [8] [9]。脑小血管病相关认知功能障碍的危险因素可分为不可控危险因素及可控危险因素, 不可控危险因素如性别、年龄等, 可控的常见危险因素包括高血压、肥胖、糖尿病等; 综上所述, 认知功能障碍与血管性危险因素之间有着密不可分的关系。本文旨在对脑小血管病相关认知功能障碍的危险因素研究进展予以综述, 为进一步探讨该病的防治提供理论依据, 以丰富脑小血管病的防治。

## 2. 不可控危险因素

### 2.1. 性别

许多神经系统疾病表现出性别差异,例如一种性别比另一种性别的患病率或严重程度更高,据报道,女性患者在 66~75 岁缺血性的发病率升高,而在其他年龄段女性的发病率均降低,与男性脑小血管病患者相比,女性患者发病的年龄大于男性患者,且脑小血管病患者中男女比例为 2.375:1 [10]。从目前的文献看,男性白质病变的发展会受到有氧运动的抑制,由此说明在不同性别中脑小血管病的典型病变存在着较大的差异[11]。男性和女性大脑在学习和记忆方面的差异,在其整个生命周期的早期发育阶段,都得到了人类和动物研究的证实。女性不仅比同龄的男性有更高的 AD 发病率,而且与年龄相关的认知能力下降速度明显快于老年男性。但尚不清楚女性比男性有更高的 AD 风险的原因[12]。可见,性别因素对脑小血管病和认知功能障碍的影响不同,因此性别在脑小血管病性认知功能障碍中的作用值得深入研究,更好地了解其中的性别差异生物学,不仅可以深入了解其预防,而且对于个性化、性别特异性医学的发展也是不可或缺的。

### 2.2. 年龄

年龄是公认的脑小血管病危险因素,伴随着年龄的增长,颅内小血管发生硬化,会造成管腔狭窄、管壁增生增厚以及脑组织灌注量的不足;同时随着年龄的增长,大脑对血流量的调节能力也会降低,从而加重脑组织的缺血缺氧,加快脑小血管病的病理过程。奥斯汀等学者认为,年龄对认知的影响可能是有以下原因:① 认知功能的下降与年龄增长呈正相关,以及脑小血管病伴发的认知功能下降与血管老化引起的认知功能下降表现相类似。② 患脑血管疾病,特别是深部白质脑病的机会伴随着年龄的增长而随之增加,且深部白质脑病与认知功能的损害高度相关[13]。

## 3. 可控危险因素

### 3.1. 高血压

高血压属于脑小血管病的独立危险因素之一,若高血压长时间没有得到有效控制,可引发颅内小动脉硬化、纤维素样坏死或玻璃样变等;同时,长期的高血压也会引起炎症因子的活化、血管通透性的增加以及血脑屏障的破坏,从而诱发脑白质病变、微出血以及腔隙性梗死等,最终导致脑组织缺血缺氧,进而引发认知功能的损害[14]。高血压相关的变化(例如,小血管病变、炎症反应、低灌注、氧化应激、自我调节过程和血脑屏障受损以及脑淀粉样血管病)可能会在脑小血管中发生,当血压控制不佳或缺乏时,可能导致认知功能降低。孤立的和同时发生的脑小血管病都会导致认知功能恶化[15]。高血压是脑小血管疾病进展和认知功能障碍的主要危险因素之一[16]。因此,对于脑小血管病患者,仔细监测和治疗高血压可能通过预防认知障碍而获益。应该更多地关注这个问题,需要有针对性地努力,提高我们对血压水平与脑小血管病进展之间的关系以及脑小血管病的数量、体积和解剖位置与认知障碍之间的关系的理解[15]。

### 3.2. 肥胖

据文献报道,肥胖患者常同时伴有数种血管性相关的危险因素,肥胖通过造成全身血管的损伤(尤其是脑部血管),进而导致认知功能的损害,使其认知功能下降[17],而且肥胖引起的炎症还可能会导致颅内微血管功能障碍,在一定程度上增加脑小血管病的患病风险。相关临床证据证实,脑小血管病发病与肥胖引发的全身多处区域脂肪的堆积有关,内脏脂肪可通过多种活性因子(如脂联素、促炎性细胞因子等)的释放从而引起凝血功能的障碍,进一步导致内皮功能紊乱,从而致使脑小血管病的患病率增加[18]。同

时,肥胖患者所摄入的高脂肪含量的食品或久坐不动会增加促炎性细胞因子的分泌[19],并通过氧化应激和细胞炎症引起心脑血管应激等非神经外周事件。据报道,肥胖与认知能力呈负相关,并随着时间的推移增加认知障碍和痴呆的风险[20]。2011年的一项 Meta 分析中发现,肥胖的人群随着体重的减轻,记忆和执行功能有了微小但显著的改善[21]。综上所述,肥胖的预防和控制对于脑小血管病性认知障碍的预防具有极其重要的意义。

### 3.3. 糖尿病

全世界约 1.71 亿人患有糖尿病,估计到 2030 年这一数字将翻一番。糖尿病的两种主要形式是 1 型糖尿病,一种自身免疫性疾病,其特征是胰岛素分泌绝对或几乎完全丧失,另一种是 2 型糖尿病,其特征为胰岛素敏感性降低和胰岛素相对不足。在这两种形式中,慢性高血糖都会导致微血管和大血管并发症。尽管大多数关注点都集中在影响肾脏、眼睛和周围神经系统的终末器官疾病上,但大脑也受到感染。糖尿病及其并发症可导致短暂或永久性认知异常以及脑小血管的不可逆病变[22]。糖尿病患病率的增加和糖尿病诊断年龄的降低表明,糖尿病相关的脑小血管病性认知功能障碍可能还会增加,并对社会产生重大影响。努力了解糖尿病相关脑小血管病性认知功能障碍的发展和进展背后的病理生理学变化,对于制定逆转或预防这些认知并发症的治疗方法至关重要。

### 3.4. 同型半胱氨酸

同型半胱氨酸(HCy)是一种含有硫醇的非必需氨基酸,是正常叶酸和蛋氨酸代谢的产物,在所有细胞中产生[23]。血浆同型半胱氨酸升高被称为高同型半胱氨酸血症(HHCy)。HHCy 是认知障碍的一个可靠和独立的危险因素[24],与病理证实的 AD 相关[25]。HHCy 与 AD 患者海马萎缩率增加[25]和认知功能减退加速相关[26],目前被认为是 AD 的危险因素[27]。据文献汇报,同型半胱氨酸水平升高是大量血管闭塞性疾病的危险因素之一[28]。此外,最近的研究表明,高同型半胱氨酸水平也与脑小血管病有关[29]。通过 Meta 分析发现,脑小血管病或脑小血管病亚型的同型半胱氨酸水平显著高于对照组,同型半胱氨酸水平升高可能是脑小血管病的危险因素[30]。B 族维生素补充剂(B6、B12 和叶酸)具有经充分验证的降低同型半胱氨酸的功效,这可能是导致脑小血管病性认知功能障碍因素中一个容易改变的危险因素[31]。因此,在进行脑小血管病性认知功能的诊断和治疗中需密切关注同型半胱氨酸水平的变化。

### 3.5. 吸烟

吸烟,即使是低剂量[32],也会增加血管疾病和中风的风险[33],为吸烟与痴呆症和认知能力下降之间的关系提供了强有力的生物学依据。烟草中所含有的尼古丁、焦油等多种有毒物质可刺激自主神经,从而引起血氧含量减少、小血管痉挛、动脉壁损伤,影响全身血液及血管系统,进一步升高纤维蛋白原水平,加速动脉硬化,促使血小板聚集等,由此可见,吸烟可加速动脉粥样硬化的进展,通过改变凝血系统功能(如增强血小板聚集性、升高纤维蛋白原、增加血细胞比容和降低 HDL-C),从而导致动脉血管内皮间隙加大,大量胆固醇及脂蛋白进入动脉内膜下层沉积并形成粥样斑块。吸烟可使脑血流量明显降低,并可加速脑动脉硬化,使脑血管舒缩功能降低,在脑小血管病的多因素作用中具有一定的影响。目前吸烟是痴呆症[34]和认知能力下降[35]的一个可改变的原因,尽管缺乏关于戒烟,特别是戒烟时机对脑小血管病性认知功能障碍的影响的研究[36],但支持与当前吸烟对脑小血管病及认知功能障碍相关的观察数据通常是一致的[34]。

## 4. 小结

脑小血管病包括脑部小动脉、小静脉、微动脉、微静脉等多处病变,并且颅内血管的病变还可能会

造成深部脑白质的功能改变, 导致脑部出现出血性变化及脑组织的损伤, 从而增加认知功能障碍的风险[37]。目前, 临床研究表明, 认知功能障碍与脑小血管病有关, 但认知功能障碍病情相对隐匿, 若不及时干预可能会进一步发展为痴呆, 严重影响患者的生活质量[38]。脑小血管病性认知功能障碍存在多种危险因素, 并且各因素之间相互作用、相互影响。血管性因素可能是老年患者脑卒中及认知功能减退诸多危险因素中最可预防的因素。因此, 尽可能早地发现并控制可干预的危险因素, 不但可以加强人们对脑小血管性认知障碍相关危险因素的认识及预防, 还可以降低脑小血管病的发病率, 延缓脑小血管病性认知功能障碍向痴呆进展以及改善患者预后, 从而减少脑小血管病的致残率, 减轻家庭及社会的负担。

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